REMARKS

Claims 245-251, 253-255 and 257-265 are pending in the above-referenced application. Claim 247 has been amended to more distinctly claim that which Applicants regard as the invention. Amended Claim 247 supported by the specification on page 65, lines 9-20 (bottom of the page), Figure 15 and example 12. Furthermore, claims 252 and 266-305 have been canceled. Applicants reserve the right to file subsequent continuation and/or divisional applications containing claims encompassing the canceled subject matter.

Applicants have also have added new claim 306 which recites a specific embodiment, a kit. New claim 306 is also supported by the specification on page 65, lines 9-20 (bottom of the page), Figure 15 and Example 12, as well as on page 58, line 16 to line 20 where it is stated:

> Kits for introducing a nucleic acid component into a cell of interest can be fashioned from this composition. Such a kit comprises in packaged containers or combinations an entity which comprises a domain to a cell of interest, wherein the domain is attached to a nucleic acid component which is in non-double stranded form. Buffers and instructions may be optionally included.

I. Substance of Interview

Applicants wish to thank Examiner J. Angell for his time and helpful suggestions during his telephonic interview with the undersigned, the Examiner's representative, Cheryl H. Agris and one of the inventors, Dr. James Donegan on May 1, 2008. The substance of the interview is discussed below.

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted pages 138 and 139 and Figure 15 for discussion purposes.

B. Identification of Claims Discussed

Proposed amended claim 247 as well as the pending claims and proposed new claim 306 were discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Meyer et al., 5,574,142 ("Meyer") was discussed.

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

The amendment of claim 247 was discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

Amended claim 247 and cancellation of claims 266-305 overcomes the prior art rejection and written description rejection. The specification and the art provide sufficient enablement for claims 263-265.

F. A General Indication of Any other Pertinent Matters Discussed

No other pertinent matters were discussed.

G. General Results or Outcome of the Interview

Applicants agreed to submit the proposed claim amendment, cancel claims 266-305 and add new claim 306. Applicants also agreed to submit references published around the priority date of the instant application showing *in vivo* administration of DNA compositions.

II. The Written Description Rejection

Claims 245-255, 257-268, 272-286, 290-303 and new claims 304, 305 are rejected under 35 U.S.C. 112, first paragraph (written description). The Office Action specifically states:

> ….. it is acknowledged that the specification does disclose several constructs, but the species disclosed are not sufficient to describe the entire genus of constructs encompassed by the claims. As previously indicated, the U1 –antisense compounds are not considered representative of the genus of instantly claimed constructs which when present in a cell produce a product where said construct has at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, the construct being bound non-ionically to an entity comprising a chemical modification or a ligand. The U1 -antisense cassette vectors do not have noncovalent polymeric interactions. Even though they are composed entirely of polynucleotides in the form of a vector, the polynucleotide units in the U1-cassette vectors are covalently bound to each other.

Applicants respectfully disagree. In Applicants view there is an adequate teaching of the subject matter recited in 245-246 in the specification. In particular, the last paragraph of page 47 states:

> Another significant embodiment of the present invention is a construct which when present in a cell produces a product, the construct being bound non-ionically to an entity comprising either a chemical modification or a ligand addition, or both. As in the case of the other above-described construct, this construct may also comprise at least one terminus, such terminus comprising a polynucleotide tail. The polynucleotide tail is hybridizable or hybridized to a complementary polynucleotide sequence. An antibody to a double stranded nucleic acid can be directed and thus bound to such hybridized polynucleotide tail sequences. The antibody can comprise a polyclonal antibody or a monoclonal antibody.

There is further support in Figure 15 and Example 12.

With respect to the teachings of the figures, the Office Action specifically states:

> The specific issue here is that the diagrams do not sufficiently describe the genus of molecules

encompassed by the claims. In other words, the schematic diagrams (i.e. the "stick figures") in the drawings do not adequately describe the chemical compositions claimed to the extent that one of skill in the art would be able to readily envisage the administration of the claimed constructs to a cell for producing a product. For instance, one of skill in the art would not be able to readily recognize the genus of species encompassed by the claims based merely on the schematic drawings, which do not clearly demonstrate adequate description of the entire genus of species encompassed by the claims. As previously indicated, the specification as filed does not adequately describe a representative number of species of the claimed invention unless one of skill in the art would be able to envisage the structure, in this case the chemical structure (nucleic acid, protein, and other claimed chemical compositions, including the cells), of the claimed invention. Since none of the examples, either prophetic or exemplified by reduction to practice, in the specification as filed provide a clear description of the genus and species within the genus of the claimed invention, one of skill in the art would not have recognized that application was in possession of a representative number of species of the claimed invention at the time the invention was made.

Applicants contend that a detailed description of the compositions of the present invention are provided on pages 48-59 The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49, and various examples of useful domains are described. Examples of various antibodies are provided in the paragraph bridging 53 and 54. These include useful domains with non-specific cell binding properties (see page53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Applicants also assert that the specification describes specific embodiments.

In response, these are not specific as they only provide general guidance as to what broad types of compositions are instantly claimed. The descriptions in both the specification and in the figures do not provide an adequate description of specific species, nor representative number of such species, of

compositions which may be envisioned to produce a product in a cell, and have an antibody component, as claimed.

Applicants disagree with the above assertions. The pending claims comprise three different elements: a domain to a cell, a domain to a nucleic acid and the nucleic acid itself. The domains are described in terms of the properties that are significant to their function. Specifically, the domain to a cell is defined as an entity having an affinity for a cell and a domain to a nucleic acid is defined as an entity having an affinity for a nucleic acid. Numerous examples of domains having properties fulfilling these requirements are given in pages 51-55. The figures are an additional part of the disclosure that present exemplifications of specific compounds that fulfill these properties. For instance, a lactyl moiety, a trilactyl moiety, and an antibody to CD34 antigen are used as illustrations of cell binding domains and a nucleic acid complementary to AAV vector DNA ("a linker DNA") is used as an example of a nucleic acid binding domain in these figures.

In Applicants view, the specific compositions of the domains are not critical features. It would be clearly evident that in the various structures shown in these schematics, the other cellular binding domains and nucleic acid binding domains described in pages 51-55 could be reasonably substituted for the ones used in these illustrations. These do in fact represent a variety of different species that are sufficiently different from each other. For instance, a cellular binding domain can comprise a ligand to a cellular receptor (a small molecule) an antibody to cellular receptor (a protein), a hormone to a cellular receptor, a virus that binds to cellular receptor (a multiprotein complex) and a lectin that binds to sugar on a cell surface. This represents a variety of very different molecules that are united by virtue of the common held property of endowing a complex to be able to bind to a target cell. In a similar fashion, the nucleic acid binding domain can be a nucleic acid that is complementary to the nucleic acid that is intended to be transported into a cell but it can also represent antibodies to nucleic acids as well as binding partners to small molecules that have been used to modify the nucleotides of the nucleic acid. Again this would represent a variety of different species of molecules that can act as domains able to bind to nucleic acids.

Furthermore, the particular nucleic acid is not a critical feature of the present invention and the teachings of the present invention should be applicable regardless of the particular sequence or purpose of the nucleic acid construct that is wished to be transported into the target cells. In order to more distinctly claim the invention claim 247 has been amended to recite that the nucleic acid component is a nucleic acid sequence desired to be delivered to the cell.

Claims 252 and 266-305 have been canceled. Claim 246 depends from claim 245 and claims 248-251, 253-255 and 257-265 ultimately depend from claim 247. Thus, arguments made with respect to claim 245 would apply to claim 246 and arguments made with respect to claim 247 would apply to claims 248-251, 253-255 and 257-265.

Thus, Applicants assert that the rejections under 35 USC 112, first paragraph (written description) have been overcome in view of the above arguments, amendment of claim 247 and cancellation of claims 252 and 266-305. Therefore, Applicants respectfully request that the rejections be withdrawn.

II. The Rejections Under 35 USC 112, First Paragraph (Enablement)

Claims 263-265, 281-283, 299-301 and claims 304, 305 have been rejected under 35 U.S.C. 112, first paragraph. It is asserted that the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (in vitro), does not reasonably provide enablement for methods of expressing a nucleic acid product in a whole organism (in vivo).

First, before responding, Applicants note that claims 281-283, 299-301, 304 and 305 have been canceled without prejudice to advance prosecution. Applicants reserve the right to file subsequence continuation and/or divisional applications on canceled subject matter.

Applicants respectfully disagree. It is Applicants view that at the time of the filing it was believed by most people that *in vitro* techniques for ligand mediated uptake would be appropriate for *in vivo* work as well. Applicants note that various domain with specific cell binding properties are disclosed in the specification on page 53, lines 10-18:

> 1) those with binding affinity for a natural cell component, epitope or ligand. Such cell binding domains include ligands specific to cell receptors such as hormones, mono- and oligosaccharides, viral proteins which recognize cell receptor sites, extracellular matrix proteins such as fibronectin and fragments thereof, antibodies to cell proteins and fragments thereof.
>
> 2) those with binding affinity for a non-naturally introduced ligand where a) the ligand is attached to a cell by chemical means such as by reaction with a tyrosine or amino group of a cellular surface protein or b) the ligand is indirectly attached to a cell non-specifically.

To further support this assertion, Applicants herewith submit as Exhibit 1 the following references describing *in vivo* administration of DNA even before the priority date of the above-referenced application, December 15, 1995:

1. Ferkol et al., 1995, "Gene Transfer into the Airway Epithelium of Animals by Targeting the Polymeric Immunoglobulin Receptor", J. Clin. Invest. 95:493-502;
2. Gao et al, 1993, "Direct *In Vivo* Gene Transfer to Airway Epithelium Employing Adenovirus-Polylysine-DNA Complexes", Human Gene Therapy 4:17-24;
3. Wu et al., 1994, "Incorporation of Adenovirus into a Ligand-based DNA Carrier System Results in Retention of Original Receptor Specificity and Enhances Targeted Gene Expression", J. Biol. Chem. 269:11542011546;
4. Wu et al., 1988,"Receptor-mediated Gene Delivery and Expression in Vivo", J. BIol. Chem. 263:14621-14624.

Applicants further note that the prior art reference cited in the instant Office Action, Meyer, has an extensive discussion of ligand mediated transport of ODNs in columns 4-6. "Systemic administration" is described in the passages of column 19 lines 38 to column 20, line 25 of Meyer as well.

In summary, Applicants assert that an enabling disclosure was provided for both *in vitro* and *in vivo* administration of the compositions of the present

invention. Therefore, Applicants respectfully request that the rejection under 35 USC 112, first paragraph (lack of enablement be withdrawn).

III. The Rejections Under 35 USC 102(e)

Claims 247-248, 250-255, 257-259, 262-263, 266, 284 and 303 are rejected under35 U.S.C. 102(e) as being anticipated by Meyer. The Office Action specifically states:

> With respect to the rejection of claims under 35 USC 102(e), Applicants argue that Meyer **does not** contain all three elements in a single composition; therefore, the claims are not anticipated by Meyer et al.
>
> In response, it is respectfully pointed out that the extracellular portion of Figure 2 teaches a non-natural entity which comprises at least one domain to a specific nucleic acid component (the antisense ODN), at least one domain to a cell of interest (the polymer carrier that interacts with the ASGP receptor), and said specific nucleic acid component (the antisense ODN). It is noted the claim does not indicate that the domain to a specific nucleic acid component and the specific nucleic acid component are required to be two different molecules. As such, the antisense ODN constitutes both the domain to a specific nucleic acid component and the specific nucleic acid component. Thus, Meyer does anticipate the instant claims.

Applicants respectfully traverse the rejection. It is Applicants' assertion that Meyer does not contain all of the elements of the pending claim. As it stands, the point advanced in the Office Action is strictly based upon considering the antisense ODN to be a domain to a specific nucleic acid of interest and simultaneously considering the ODN to be the specific nucleic acid of interest itself. In Applicants view, this concept is not reflected in the claim language itself where it specifically states "at least one domain **to** a specific nucleic component" indicating that the affinity of the domain is towards the specific nucleic acid component. Applicants do not believe that this should be interpreted as the domain and the nucleic acid being one and the same. Applicants note that on

page 51 of the instant application, a definition is given "A domain is an entity that has a segment that **binds** either to a cell or to a Nucleic Acid Component". Thus in a composition that comprises a specific nucleic acid component and an entity that comprises (a) a domain to a cell and (b) a domain to the specific nucleic acid of interest, the binding between the entity and the nucleic acid component is meant to result in the domain to the cell now being joined to the specific nucleic of interest by means of the domain to the nucleic acid. This is reflected in various passages of the specification as well as numerous illustrative Figures. Although Applicants concede that the ODN of Meyer has a domain **to** a specific nucleic acid, Applicants asserts that this specifies interaction between an ODN and its intended mRNA target with the mRNA fulfilling the role of 'specific nucleic acid component". Although Applicants believe the language of the claim presently describes "a domain to a specific nucleic acid component" and the "specific nucleic acid component" are separate interacting entities, Applicants have amended claim 247 to more distinctly recite this concept by adding the following to the end of the claim: "wherein said specific nucleic acid component is bound to said entity through said domain to a specific nucleic acid component.' Thus, clearly, amended claim 247 is not anticipated by Meyer.

Applicants note that claims 252, 266, 284 and 303 have been canceled. Further, Applicants note that claims 248, 250-251, 253-255, 257-259 and 262-263 ultimately depend from claim 247. Thus, Arguments made with respect to claim 247 would apply to these claims as well.

In view of the above arguments, the amendment of claim 247 and the cancellation of claims 252, 266, 284 and 303, Applicants assert that the rejection under 35 USC 102(e) have been overcome. Therefore, Applicants respectfully request that the rejections under 35 USC 102(e) be withdrawn.

IV. Conclusion

Applicants assert that the claims are in condition for allowance. If a telephone conversation would further the prosecution of the present application,

Applicants' undersigned attorney request that he be contacted at (9140 712-0093.

Respectfully submitted,

/Cheryl H Agris/

Dated: August 24, 2008

Cheryl H. Agris, Reg. No. 34,086